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Alzheimer's disease pharmacotherapy, biomarkers and genetics

Abstract

This Alzheimer 's disease review has a focus on historical, statistical, financial, and genetic disease factors. Genetic research, particularly the TOMMOROW study, as well as its theoretical bases, is reviewed. Select cognitive and adjunctive pharmacotherapies that are currently prescribed in these dementia patients are discussed. Both the inherited and sporadic types are reviewed, as well as the theoretical basis for current treatment of Alzheimer's disease. Prevalence, both current and projected, is also discussed. Bio-markers identified as useful in the detection of Alzheimer's dementia and their potential usefulness in earlier intervention are also covered in this review.

Keywords: Alzheimer's disease, Review, Dementia, Financial, Genetics, Pharmacotherapies, Prevalence, Bio-markers, Prevention

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia and loss of intellectual function among people 65 years and older. According to the Alzheimer's Foundation of America.[1] AD is a progressive, degenerative disorder that attacks the brain nerve cells, or neurons, resulting in loss of memory, thinking, language skills, and behavioral changes.[2,3] This disease does not, though, constitute part of the normal aging process. Identified is research currently being conducted to identify the root cause of AD, develop mechanisms for its treatment and prevention as well as to delay the progressive clinical manifestations. Reviewed are the factors related to AD onset, prevalence, and categorical types and their characteristics. Also reviewed is the current pathophysiological hypothesis, as well as the pharmacological therapies widely prescribed for this dementia's treatment.[4] Bio-markers, prevention, and environmental factors are discussed.

Onset and Prevalence

First described by, and later named after, a German psychiatrist and pathologist Alois Alzheimer, this disease's existence was identified in 1906. Presently, AD accounts for 60-70% of prevalent dementia cases. Categorized as a chronic neurodegenerative disease, AD usually starts slowly and progressively worsens over time. The most common early symptom is short-term memory loss. In 2010, there were between 21 and 35 million people worldwide with AD; this number is approximate because an autopsy is required to definitively diagnose AD. Approximately 70% of the risk is believed to be from genetic disposition. Other risk factors include a history of head injuries, depression, or hypertension; it appears that genetics could hold the much needed insight of the disease.[5] The majority of AD cases (95-96%) have an onset that begins over 65 years of age, while only 4-5% of cases are considered early-onset Alzheimer's that begins before the age of 65.[6] About 6% of people 65 years and older are affected by AD. In 2010, dementia resulted in about 486,000 deaths.

Inherited and Sporadic Types

Alzheimer's disease is categorized as two different types, the first of which is a familial (inherited) AD.[7] Most of the cases of autosomal dominant familial AD can be attributed to mutations in one of three genes: Those encoding for amyloid precursor protein (APP) on chromosome 21, and presenilins 1 and 2. Amyloid precursor protein was the first discovered gene with mutations that was found to cause inherited AD. Presenilin-1 (PS-1) and Presenilin-2 (PS-2), was the second gene with mutations which was identified as a cause for early onset AD. Apolipoprotein E-e4 (APOE4) was the first gene variation found to increase the risk of AD.[8,9] Most mutations in the APP and presenilin genes increase the production of a small protein, Aβ42, which is the main component of senile plaques. The increasing amount of these plaques are thought to be directly associated with the onset of AD. If one of these mutated genes is inherited from a parent, this person will almost always develop early onset Alzheimer's disease.

The second type is the sporadic Alzheimer's disease, illuminating that there is no single known cause. This type of Alzheimer's usually develops after 66 years of age and is referred to as late onset AD, the etiology of which shows no obvious inheritance pattern. In some families, however, clusters of cases have been seen. Most cases of Alzheimer's disease do not exhibit autosomal dominant inheritance, although environmental and genetic differences may act as risk factors. The best known genetic risk factor is the inheritance of the E4 allele of the apolipoprotein E (APOE) on chromosome 19. Between 40 and 80% of people with AD possess at least one APOE4 allele. The APOE4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes. Like many human diseases, environmental effects and genetic modifiers result in incomplete penetrance. For example, certain Nigerian populations do not show the relationship between dose of APOE4 and either incidence or age of onset for AD, as seen in other human populations.

Cognitive Pharmacotherapy

Alzheimer's disease (AD) pathogenesis has been theorized to be caused by a deficiency of cholinergic neurotransmission. Treatments for Alzheimer's dementia are initiated to enhance cholinergic neuro-transmission, provide anti-oxidant supplementation for neuro-protection, and or antagonize NMDA neuro-receptors. Aricept (donepezil) is a cholinesterase inhibitor, for example, whose mechanism of action is postulated to reversibly inhibit acetylcholinesterase hydrolysis, which should then result in enhanced cholinergic function.[10] Razadyne (galantamine) is an anticholinesterase inhibitor. Exelon (rivastigmine) is a parasympathomimetic (cholinergic) agent.

Namenda (memantine) is an NMDA receptor antagonist. The result of increased function is an improvement of behavior, cognition, and daily living activity functional abilities, which have been clinically documented and anecdotally observed. Of note, though, is that there is no current treatment that has prevented the inevitability of the cerebral neurodegeneration inherent in AD progression.[11] Presumably, that lack of prevention related to the neurodegeneration is the result of the progressive amyloid deposition and tau protein accumulation damage, for which no current treatment (including Aricept) has been targeted toward or proven to be effective. It is instructive to recognize that psychoactive medications often disrupt the patient's thermoregulation, leading to an increased risk of heat-related injury.

Adjunctive Pharmacotherapy

For behavioral changes conditions, frequently prescribed are antidepressants (citalopram, sertraline, and fluoxetine), anxiolytics (lorazepam and oxazepam), and antipsychotics (haloperidol, quetiapine, and risperidone). The adjunctive medications are used in combination with each other as well as with the medications for cognitive treatment, effectively creating a drug cocktail that only treats the symptoms, not the disease itself.

As identified by Mayo Clinic (2014), many drugs utilized just for the control of associated AD dementia symptoms. Discussed will be several of those drugs and the potential for negative outcomes when prescribed to dementia patients. Use of several of these drugs should be closely supervised, and prescribed with extreme caution. They would be counterproductive to the treatment goal for AD patients, which is the improvement of cognition. This class of drugs would also present a potential for safety issues.

Ativan (lorazepam) is a benzodiazepine (BZD) tranquilizer that is primarily indicated for the treatment of anxiety, with a sedative action that diminishes cognition. The BZD class of drugs should not be used to treat patients who already have cognitive impairment such as is present a dementia patient.

Norpramin (desipramine) is a tri-cyclic antidepressant (TCA) that inhibits the re-uptake of norepinephrine (NE), and to a lesser extent, serotonin (SE). Norpramin is indicated for the treatment of depression, and also has a sedative effect that results in cognitive impairment. Additionally, Norpramin's side effects of impulsivity, irritability, agitation, hostility, and aggressiveness, likely would exacerbate those same symptoms already caused by progressive AD. This drug would be counterproductive to the treatment goal for AD patients and might also be dangerous to the safety of the patient.

Haldol (haloperidol) is a major anti- psychotic that decreases brain excitement and is indicated for the treatment of schizophrenia as well as for controlling Tourette's syndrome motor and verbal symptoms (tics, utterances). The precise mechanism of action is not known. Haldol has anti-cholinergic side effects that include dry mouth, drowsiness and anxiety. This drug will not meet the treatment goals related to increased cholinergic activity, and likely would actually worsen the cognitive symptoms through the anti-cholinergic action. There is also a black box warning, that there is an increased risk of death in older adults who are treated with Haldol.

Zoloft (sertraline) is a selective serotonin re-uptake inhibitor (SSRI) anti-depressant that is indicated for the treatment of major depressive disorder, obsessive-compulsive disorder, panic attacks, social anxiety disorder, premenstrual dysphoric disorder, and post-traumatic stress disorder. While Zoloft has no significant (<1%) anticholinergic effect, it also does not improve cholinergic activity. Side effects of agitation, anxiety, insomnia, and nervousness were also reportedly insignificant (<1%). This drug will not improve function in the AD patient, and has the potential to exacerbate symptoms.

Melatonin available for purchase is usually a synthetic version of the natural Pineal Hormone, and is likely to be helpful for certain types of sleep disorders. This hormone/drug does not affect the cholinergic activity and has no known anti- oxidant neuro-protectivity. Melatonin regulates day-night and sleep-wake cycles. Natural production/ reduction of systemic melatonin is directly dependent upon darkness/ light conditions. The drug causes sleepiness, which can occur during the daytime hours. Reduction of cognitive function is associated with sleeping/sleepiness. Melatonin, therefore, would not be indicated and might cause safety issues.

None of these options has an indication in the treatment of AD dementia as related to a potential for slowing the progression, improving, or curing, of this disease. None of these drugs affect the tau protein accumulation or the amyloid deposition within the brain. Neither do any of the drugs listed affect acetylcholine synthesis, re-uptake, or systemic levels, under which the current AD pathophysiologic hypothesis is based. There are a couple of drugs listed that could be utilized for ancillary symptom control, however, none of them has an indication for treatment of the AD progressive cognitive dysfunction itself.[10]

Research

There is a compelling likelihood that as investigative research of genetic risk factors proceeds, identified will be a stronger correlation between environmental risk factors predisposing patients to AD and environmental effects that potentiate or accelerate the course of this disease. The main focus of research is directed at the genetics factors. The TOMMORROW study is currently in clinical trials and is based on two theories. The first, from the neurologist Warren Stritmatter, who postulates that a molecule called apolipoprotein E (ApoE) seemed to contribute to AD by promoting two pathways in the brain: Amyloid-B deposition in the brain and ApoE repair mechanism for neurons under stress that has no amyloid association, The bad ApoE4 form tends to be broken down in toxic fragments that damage the cell's energy factories (mitochondria) and alter the cell skeleton. The next study, by geneticist Allen Rose and his team, described a stretch of non-coding DNA in a gene called TOMM40 that sits next to ApoE on chromosome 19. This discovery was important because the protein encoded by TOMM40 (named Tom40) is crucial to healthy mitochondria. The Tom40 forms a channel in the outer mitochondrial membrane that is used to import proteins. Due to these findings, and the interest of genotyping both the ApoE and TOMM40, two pharmaceuticals have joined forces to evaluate these findings on clinical trials. This trial also will investigate whether a low dose of pioglitazone (already approved at much higher doses for type 2 diabetes treatment) can delay disease onset in those individuals deemed to be at high risk of AD. Evidence from animal and small scale human studies suggest that pioglitazone may prevent or reverse AD-related pathology and symptoms.[12] As technology advances and knowledge expands related to the initiative, as well as study investment by these researchers and the junction of forces and funding of visionary pharmaceutical companies, new and potentially better resources and treatments will be on the horizon to sustain and prolong the patients' quality of life.

Financial Costs

Wadman.[13]reported that brain tissue damage due to the effects of AD dementia has been conclusively determined to begin 10-15 years

prior to the onset of clinical symptoms. Hebert et al.[14] reported that the increase in prevalence has been projected to be as much as 400% just in the United States population, by the year 2050. The authors quantified the projected prevalence to equate to 13.8 million people afflicted with AD by the year 2050, 7 million of whom are expected to be aged 85 or older. The resultant financial cost just in health care expenses has been projected to exceed $1Trillion per annum.

Bio-markers

There are no known curative or preventative measures to address this devastating disease's onset or progression, according to Wadman.[13] Prevention and interruption of the progression of the dementia are two critical factors to consider. Early detection is a key to early diagnosis and implementation of treatment, in an attempt to limit or delay the dementia advancement. Boyle.[15] identified three important biomarkers for the early identification of AD, the occurrence of which was reported to be years to decades prior to the onset of cognitive symptoms: Amyloid accretion (5-20 years), tau accumulation (1-5 years), and cell atrophy that results in reduced brain size (1-3 years). Boyle also described lifestyle correlates that may well be precursors to the onset of, or an impetus to worsening of AD symptoms. Many of these related to circadian rhythm disruption, which was reported to affect every metabolic pathway, and have profound manifestations physiologically and behaviorally. The commonality of these correlates was that there is a resultant metabolic, immunologic, and cognitive dysfunction.

Conclusion

Boyle's discussion also lends credence to the ability to prevent AD and its progression or severity through lifestyle modifications, contradicting Wadman's.[12] statement that preventive measures are unknown. Normal aging processes do not lead to inevitable dementia. Future research, focused on primary prevention related to the systemic dysfunctions identified by Boyle, is critical. Pharmacotherapies and natural treatments that will positively influence the prevention and progression of AD need to be identified or developed. Safety in prescribing to this population must be at the forefront for every prescribing provider. Clearly, an aging population has the potential to be a devastating financial impact to health costs related to treating those who are, or are projected to be, afflicted with AD. This review highlights the importance of focusing research efforts on early diagnosis via bio-marker and other screening methods, as well as early recognition and immediate correction of the aforementioned lifestyle and environmental risk factors. The authors have no conflicts of interest to disclose.

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Conflicts of interst

None.

References

1. http://www.alzfdn.org/AboutAlzheimers/definition.html
2. https://www.nia.nih.gov/alzheimers/publication/alzheimers–disease–fact–sheet#symptoms
3. Burns A, Iliffe S Alzheimer's disease. *BMJ*. 2009;338: b158.
4. WHO Dementia. Fact sheet N°362, World *Health Organization, Geneva, Switzerland*. 2012
5. Brown T, Larsen E Psychoactive medications as independent risk for heat injury in emergency medical service workers. *International Journal of Emergency Mental Health and Human Resilience*. 2015;17(1):189–190.
6. Mendez MF Early–onset Alzheimer's disease: Non–amnestic subtypes and type 2 AD. *Arch Med Res*. 2012;43(8):677–685.
7. Waring SC, Rosenberg RN Genome–wide association studies in Alzheimer disease. *Arch Neurol*. 2012;65(3):329–334.
8. http://www.alz.org/alzheimers_disease_causes_risk_factors.asp#genetics
9. Mahley RW, Weisgraber KH, Huang Y Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2006;103(15):5644–5651.
10. http://www.rxlist.com/drugs/alpha_a.htm
11. Robbins SL, Cotran RS, Kumar V, et al.Pathologic basis of disease (6th edn), W B Saunders Company, *Philadelphia, USA*. 1999
12. Hall K, Murrell J, Ogunniyi A, et al. (2006) Cholesterol, APOE genotype, and Alzheimer disease: An epidemiologic study of Nigerian Yoruba. *Neurology*. 1999;66(2):223–227.
13. Wadman M US government sets out Alzheimer's plan. *Nature.* 2012;485(7399):626–627.
14. Hebert LE, Weuve J, Scherr PA, et al.Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*. 2013;.80(19):1778–1783.
15. http://www.cogsci.ucsd.edu/~mboyle/COGS11/COGS11–website/pdf–files/18–S15–COGS11–Alzheimers%20Disease.pdf